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Computational Design of Highly Potent Organic Superbases

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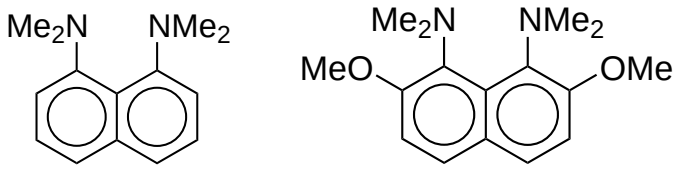
A systematic computational study of the basicity of neutral organic molecules is carried out. It has led to the Aufbau Prinzip for tailoring of strong superbases, which proved very useful in practical applications. The most important effects used for this purpose are the cationic resonance, aromatization and the aromatic domino effect triggered by protonation. Very useful devices, either for fine tuning or for significant amplification of the basicity, are provided by the substituent and intramolecular hydrogen bonding corona effects. Since a parallel investigation of the design of neutral organic superacids is completed too, it appears that a strong overlapping between superacids and superbases is achieved in the region between 255 and 300 kcal/mol. This is a prerequisite for studying spontaneous proton transfer between superacids and superbases and formation of stable ion pairs. The latter might well lead to new features and novel materials of high practical value.

1 Introduction

Notwithstanding its very small size, the proton plays a gargantuan role in chemistry and biochemistry[1,2], in particular in the proton transfer reactions. According to Broensted, the proton defines the acidity and basicity of chemical substances. Thus, acids are compounds which release the proton, whereas bases are compounds which absorb it. The interplay between acids and bases lies at the heart of chemistry. It is, therefore, not surprizing that a lot of research interest was devoted to syntheses of strong bases and superbases. Particular attention has been focused on the preparation of the neutral organic superbases and proton sponges, which in turn soak the protons as the sponges absorb the water. Neutral organic superbases have a distinct advantage in this respect compared to their inorganic counterparts, because they are non-ionic and consequently require milder conditions in chemical reactions[3]. In addition, they possess much better solubility and higher stability at the same time[4]. The first proton sponge was synthetized some thirty years ago by Alder et. al.[5], named in a shorthand notation DMAN **1**. It is schematically shown in Fig. 1.



1 **2**

Figure 1. Alder's proton sponge DMAN **1** and its more basic derivative **2**.

Since then a number if its offsprings were prepared and discussed in the literature[6,7]. A representative example is given by the compound **2**, depicted in Fig 1, which includes two methoxy groups. It can be computationally shown that **2** is more basic than **1**. However, it became clear to us that this family of compounds is of little value, if superstrong bases are desired. Obviously, new approach and concepts were needed in order to develop a new strategy in designing ultra–strong neutral organic superbases. Therefore, we have undertaken a systematic study of the underlying principles governing the basicity of molecules, which would then serve as the guiding ideas in tailoring superbases. It turned out that the chemical systems of interest were sizeable and computationally highly demanding. A valuable help in this respect was provided by the Central Institute for Applied Mathematics (ZAM) within the John von Neumann Institute for Computing (NIC) by generous donation of the computational time on the hardware platform CRAY J90. Our main achievements so far are outlined in the following sections.

2 Motivation

The aim of this research is to design strong organic (super)bases *in silico*, which will span proton affinities between 250 and 300 kcal/mol in the gas phase. Our calculations will identify a number of different families of organic compounds, which are good candidates for superbases thus representing useful targets for synthetic work. In pursuing our goal we shall try to extend the existing ladder of basicity by adding as many rungs as possible, which are as dense as possible at the same time. Molecules with PA values close to 300 kcal/mol or higher would enter the ladder of acidic compounds meaning that both acidity and basicity scales would merge into a unique ladder. The latter could be conveniently termed as Jacob's ladder of acidity and basicity. This would be of great importance in chemical research, since one could study very strong hydrogen bonds (VSHB) between superacids and superbases, spontaneous proton transfer and formation of ion pairs exhibiting completely new features, which might be both scientifically interesting and useful in practical applications[9,10].

3 Theoretical Framework

A convenient measure of basicity is proton affinity of the neutral base. It is defined as:

$$PA(\mathrm{B}_\alpha) = (\Delta E_{\mathrm{el}})_\alpha + (\Delta ZPVE)_\alpha \tag{1}$$

$$(\Delta E_{\mathrm{el}})_\alpha = E(\mathrm{B}) - E(\mathrm{BH}^+_\alpha) \tag{2}$$

$$(\Delta ZPVE)_\alpha = ZPVE(\mathrm{B}) - ZPVE(\mathrm{BH}^+_\alpha) \tag{3}$$

Here, B and BH^+_α denote the base in question and its protonated form, respectively, whilst α stands for the site of proton attack. Eqns. (2) and (3) give the electronic ($\Delta \mathrm{E}_{el}$) and zero point vibrational ($ZPVE$) contributions to the proton affinity, respectively. It should be mentioned that the electronic energy ($\Delta \mathrm{E}_{el}$) includes the nuclear repulsion term, whereas $(\Delta ZPVE)_\alpha$ describes a change in the vibrational energy upon protonation. This is understandable, because the protonated base (or in chemical terminology conjugate acid) has

an additional atom and an additional chemical bond implying that its vibrational energy is different. Theoretical methods used in the calculations of proton affinities will not be discussed in detail, because they are just a tool in tailoring strong organic superbases. However, it is important to point out that we employed the modern ab initio and density functional (DFT) methods. The theoretical models of choice were carefully tested first against some available experimental data. They represent the best possible compromise between practicability on one side and realiability on the other. Both aspects are equally important since we would like to get predictive results in quite large chemical systems. Finally, it should be mentioned that mathematical technology behind our work is described in the GAUSSIAN suite of programs[11].

4 Results

In this section we shall briefly describe the most important findings. For a better understanding of the forthcomming results we shall present first the Aufbau Prinzip we develop in designing very strong organic superbases, which serves as Ariadne's thread in attaining prescribed goals.

4.1 The Aufbau Prinziple of Superstrong Organic Bases

The set of steps to be undertaken in tailoring superbases forms the Aufbau Prinzip, which is epitomized below:

I. Choice of the appropriate skeleton subunit
   (a) selection of a functional group possessing high intrinsic basicity (imine, ylide,....)
   (b) formation of a molecular backbone carrying the highly basic center
      (i) polyguanides, phosphazenes, ylides... (the cationic resonance effect)
      (ii) cyclohexadienimine, iminocyclopropane, iminodihydropyrolimine... (the cationic aromatization or the aromatic domino effect)

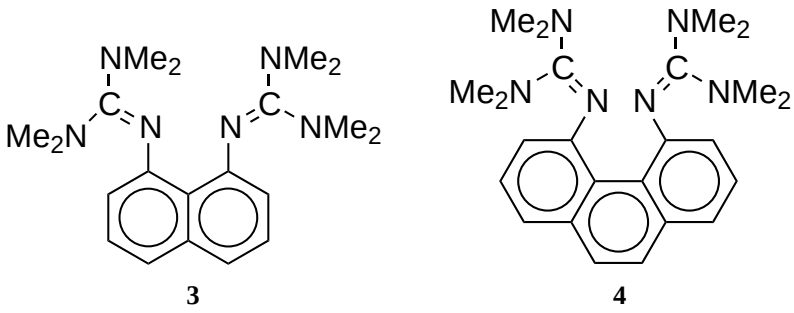
II. Modulation - insertion of right substituents at strategic sites
   (a) sigma-electron donors: alkyls....
   (b) pi-electron donors: NMe_2, OMe .....

III. The buttresing effects:
   (a) steric and angular strain in the initial base
   (b) intramolecular hydrogen bonding (IMHB) effect
   (c) IMHB corona effect in the conjugate acid

The procedure involves identification of the functional group exhibiting high intrinsic basicity (e.g. MeN=), selection of suitable molecular fragments serving as carriers of the functional groups of choice, fine tuning of the basicity by placing suitable substituents at appropriate positions and use of some special effects like for example IMHB. We have shown that this strategy should lead to a large catalogue of powerful bases and superbases.

4.2 Climbing Jacob's Ladder of Superbases

Extensive calculations performed on a large variety of widely different functional groups revealed that imine nitrogen is a very good proton acceptor. The next logical step was to introduce two guanidine groups at positions 1 and 8 in naphthalene in full analogy with DMAN. It's tetramethyl derivative TMGN **3** depicted in Fig. 2 was predicted to be more basic than the paradigmatic DMAN proton sponge. This compound (TMGN) was syn-

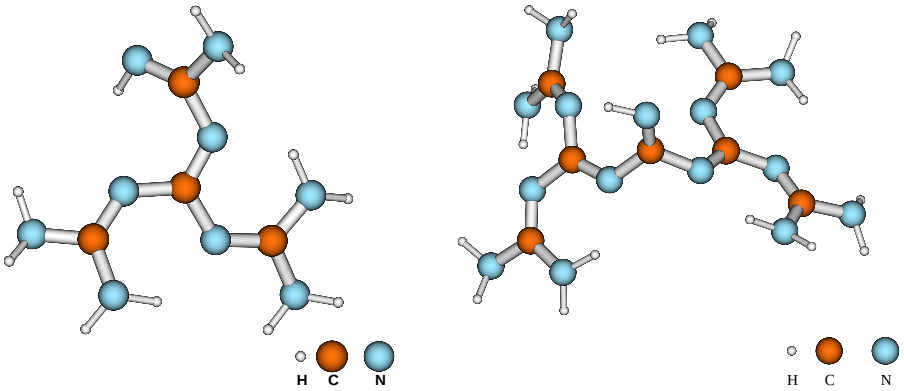


3 **4**

Figure 2. New proton sponges: synthetized TMGN (**3**) and TMGP unsythetized as yet **4**.

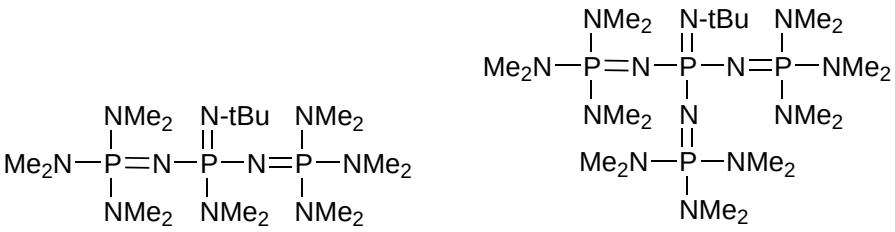
thetized by Raab et al[12]. It was found that TMGN had a number of advantageous properties as a proton sponge including favourable kinetics. Its proton affinity was calculated to be 257.5 kcal/mol, whereas its pKa turned out to be 25.4 in acetonitrile[13], which favourably compared with the measured value 25.1 ± 0.2[12]. An important finding is that the IMHB is asymmetric meaning that the proton is attached to one imine nitrogen of the let us say first guanidine group. Interestingly, its vis-a-vis nitrogen partner is semiprotonated via IMHB as evidenced by a resonance effect in the second guanidine group. The latter acquires a resonance stabilization, which is almost 50% of that occuring in the first guanidine fragment. Optimization of the molecular backbone, which in turn directly affects IMHB, indicates that compound **4** (Fig. 2) achieves the highest proton affinity in this family of compounds (PA = 268.2 kcal/mol)[14].

Since the cationic resonance effect in the protonated forms is obviously very important in stabilizing the conjugate acids, we considered polyguanides **5** and **6** Fig. 3 as examples *par excellence* for extended pi-systems[15]. It appeared that more branched systems are more basic as evidenced by the PA values of 261.8 and 285.0 kcal/mol for **5** and **6**, respectively. There is no doubt that permethylation of these molecules would further increase basicity of these systems. It is interesting to mention that phosphazenes are more basic than the corresponding polyguanides. There are several reasons for that, one of them being the larger number of NMe_2 groups that can be accomodated around phosphorus atoms. Consequently, PA values of 288.8 and 297.5 kcal/mol estimated for phosphazenes **7** and **8** (Fig. 4), respectively, are very high indeed[16]. A new and interesting structural and electronic motif is provided by quinoid molecule **9** (dimethylamino derivate of 4(1H)-piridinimine)[17] shown in Fig. 5. It undergoes aromatization upon protonation by forming the pi-electron sextet within the six-membered ring. Remarkably enough, this small compound is very basic as evidenced by a high PA value (264.6 kcal/mol). The idea of



5 **6**

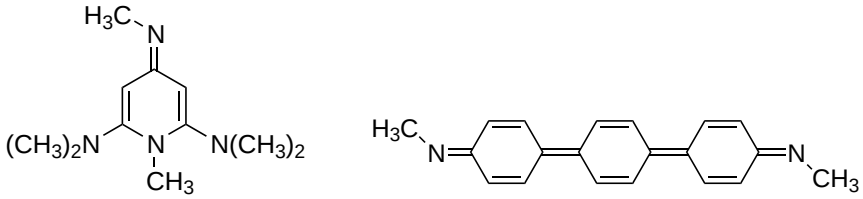
Figure 3. Highly basic tetraguanide (aminoimine manxane) **5** and heptaguanide (octopus) **6**.



7 **8**

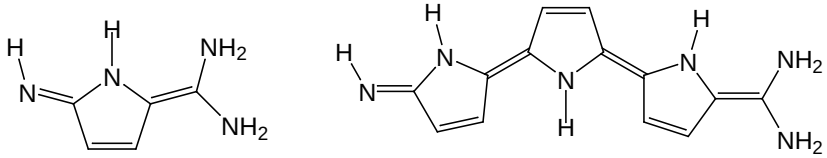
Figure 4. Schwesinger's phosphazenes *t*Bu–P3 **7** and bifurcated *t*Bu–P4 **8**.

aromatization can be straightforwardly generalized and materialized in polyquinoid system like **10** (Fig. 5), where the **aromatic domino effect** takes place. All six-membered rings are aromatized upon protonation of the imine nitrogen. They form almost ideal benzene rings, which are twisted relative to each other by some 30 degrees. The concept of aromatization triggered by protonation is quite general. As an another example we give



9 **10**

Figure 5. Molecules **9** and **10** undergoing aromatization and the aromatic domino effect, respectively, triggered by protonation.

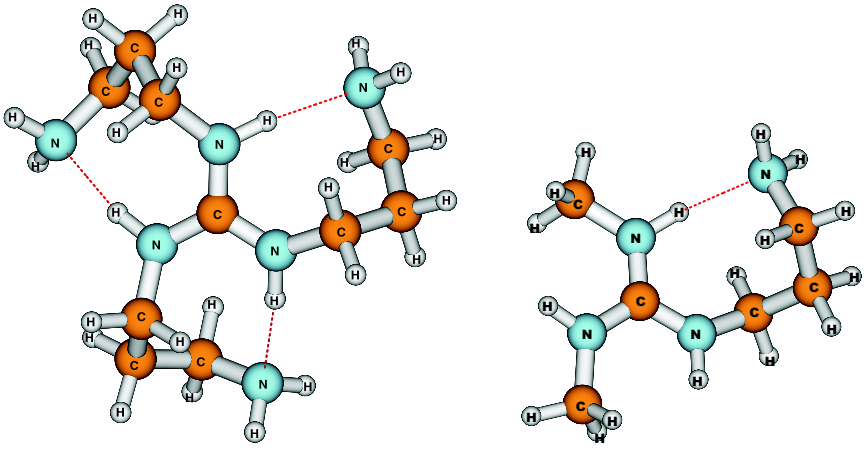


11 **12**

Figure 6. 2,5-dihydropyrrolimine **11** and its extended form **12**.

2,5-dihydropyrrolimine **11** and its extended from **12** (Fig. 6), which have high PA values of 257.0 and 282.8 kcal/mol, respectively. Examination of the structural parameters (bond lengths) and distribution of pi-electrons in the latter molecule confirms a plausible assumption that the aromatic effect propagates along the juxtaposed five-membered rings in a domino fashion without any problems[18].

A very interesting motif is given by the IMBH corona effect. It is realized by the aminopropyl side chain attached at the imine nitrogen to be protonated. A pseudo-six-membered ring is formed upon the protonation via hydrogen bonding between the amino group of the chain and the proton bound to the imine N atom. It contributes about 7-8 kcal/mol to the stability of the corresponding conjugate acid[19]. An extension of this idea is N,N',N"–tris(3–aminopropyl)guanidine **13** possessing three aminopropyl groups capable of forming IMH bonds and its "younger brother" **14** involving just one aminopropyl group (Fig. 7). Obviously, the PA of **13** is significantly higher than that of **14** (268.4 vs. 254.4 kcal/mol) due to a collective effect of three IMHBs[20]. Let us mention at the end that the basicity can be considerably amplified by judicious choice of some convenient substituents placed at specific positions in the initial molecule. They influence the proton affinities in several different ways e.g by affecting Koopmans' ionization potential, the relaxation effect exemplified by the cationic resonance effect, aromatization etc. This is very



13 **14**

Figure 7. Collective IMHB effect in N,N',N"–tris(3–aminopropyl)guanidine **13** and a single corona effect in **14**.

well described by a trichotomy formula[21,22], which we frequently use as a guidance in our work.

Melting of all ideas expounded above coupled with massive computations has led to a ladder of strong neutral organic superbases, which entered the realm of strong mineral superacids (Fig. 8). It should be mentioned that each point on the right hand side of the lad-

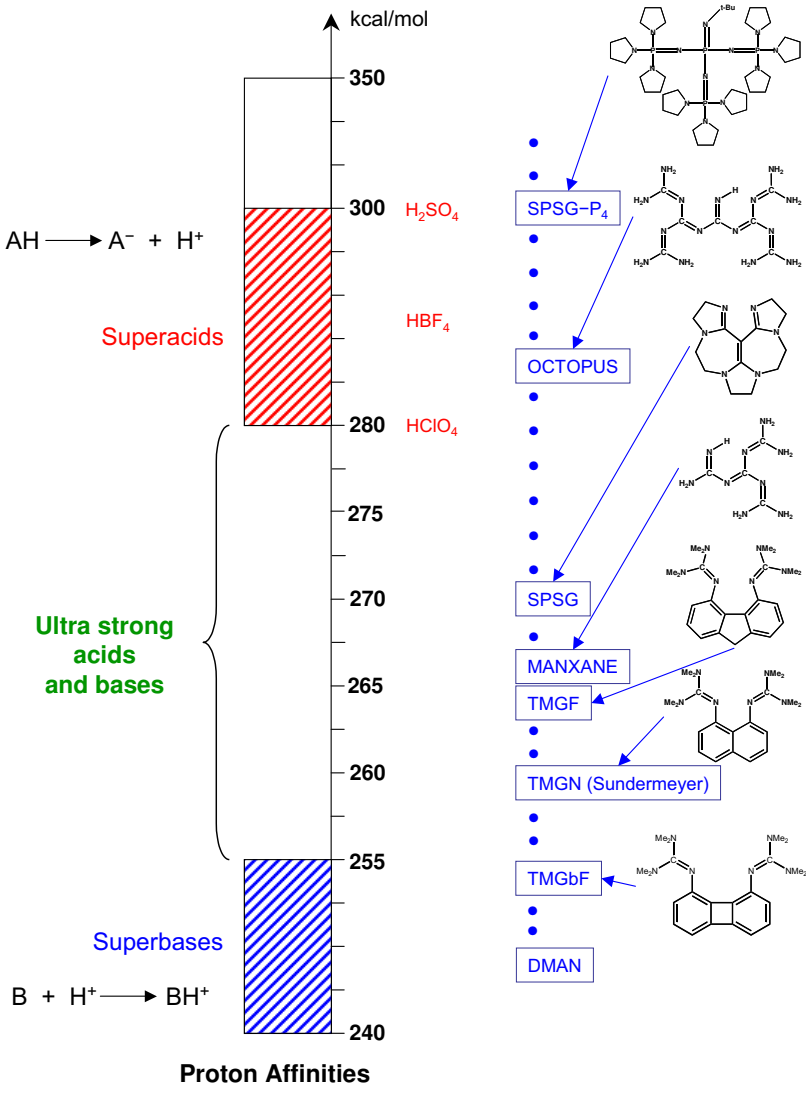


Figure 8. Jacob's (unified) ladder of acids and bases.

der corresponds to a strong base with the theoretically predicted proton affinity represented by this point. Some of these compounds are synthetized already like TMGN, vinamydine SPSG and Schwesinger proton sponge P4 (SPSG-P4). Others are waiting to be prepared in a laboratory. It is important to stress that a set of ultrastrong neutral organic superacids are also predicted by computational methods and that they descend Jacob's ladder of proton affinities to a PA value as low as 255 kcal/mol[23]. It can be said that merging of two scales of acidity and basicity is accomplished already *in silico* and that a single unified ladder is formed. It is just a matter of time when true compounds will be synthetized in laboratories.

4.3 The Origin of Basicity - Trichotomy Formula

The role of theory is to predict new features and phenomena and to help experimentalists in revealing the secrets of Nature. However, a very important task is to provide rationalization and interpretation of both computational and measured data too. Only in this way we can understand the natural laws governing behaviour of the Universe.

The question of the origin of acidity and basicity is of considerable relevance in chemistry. Which molecular features and mechanisms make one substance more basic (or acidic) than some others? The answers are provided by a trichotomy formula developed recently[21,22]. The point of departure is the well known formula derived form the thermodynamic cycle:

$$(PA)_\alpha = (BAE)^+_\alpha - (IP)^{\rm ad}_1 + EA({\rm H}^+) \tag{4}$$

where $(BAE)^+_\alpha$ gives the bond association energy of the homolytic bond formation between the radical cation $B^{+\bullet}_\alpha$ and the hydrogen atom, $(IP)^{\rm ad}_1$, signifies the first adiabatic potential describing ejection of the least bound electron, whereas $EA({\rm H}^+)$ is the electron affinity of the proton being 13.6 eV. Eqn.(4) has two drawbacks: (a) the first adiabatic potential $(IP)^{\rm ad}_1$ involves an amount ot the electron density reorganization, which is not negligible and (b) the lone pair to be protonated sometimes does not correspond to the least bound electrons in a molecule. In other words, the $(IP)^{\rm ad}_1$ potentials do not yield the best possible description of the initial base. The latter is, however, provided by Koopmans' ionization potentials $(IP)^{\rm Koop}_n$, which are calculated within the clamped nuclei and frozen electron density approximation. It should be also noticed that $(IP)^{\rm Koop}_n$ gives the n-th ionization potential i.e. that it is related exactly to that electron, which participates in the bond formation. Hence, Koopmans' IP mirrors a true electronic structure of the initial base in the Hartree-Fock model. This is very important because in our picture the electron is ejected first in view of a very high electron affinity of the incomming proton. Subsequently, the base is relaxed before it is reached by the newly formed hydrogen atom and, finally, a bond between the molecular cation and hydrogen atom is formed thus completing the protonation process. The corresponding trichotomy formula[21] reads:

$$(PA)_\alpha = -(IP)^{\rm Koop}_n + E({\rm ei})^{(n)}_{\rm rex} + (BAE)^+_\alpha + 313.6 \qquad kcal/mol \tag{5}$$

where the relaxation energy upon the ionization is given by:

$$E({\rm ei})^{(n)}_{\rm rex} = (IP)^{\rm Koop}_n - (IP)^{ad}_1 \tag{6}$$

It should be mentioned that eqn.(5) offers in principle exact proton affinites meaning that all imperfections are due to approximations inherent in computations. A similar formula holds for the deprotonation energies alias acidity[22].

Let us illustrate application of formulas (5) and (6) in considering the proton affinities of methylenimine (CH_2=NH) and guanidine ((NH_2)$_2$C=NH). It is very well known that the latter compound is much more basic and it would be interesting to learn about the reasons behind this difference. The highest occupied molecular orbital (HOMO) in CH_2=NH is the lone pair (Fig. 9), as one would intuitively expect.

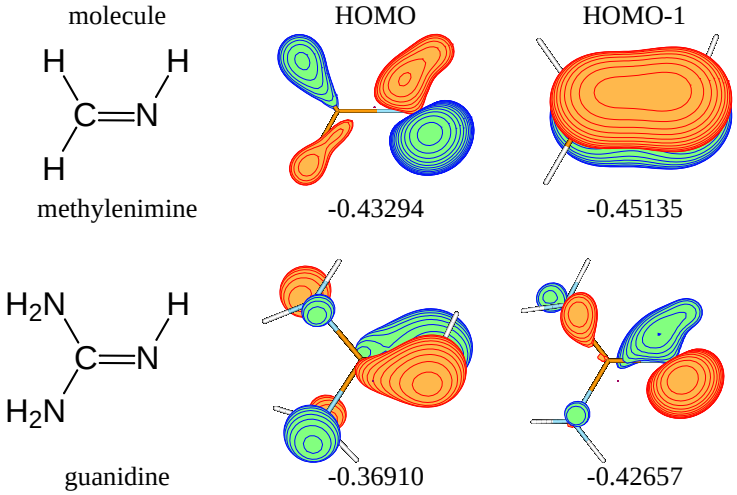


Figure 9. Pictorial representation of HOMO and HOMO-1 in some characteristic molecules.

However, an inversion takes place in guanidine,where the lone pair is placed in HOMO-1, which is shifted below the C=N π–double bond. In spite of that, $(IP)_2^{\mathrm{Koop}}$ is somewhat higher (by 4 kcal/mol) than $(IP)_1^{\mathrm{Koop}}$ in CH_2=NH. This means that the price to be paid in ionizing the lone pair in guanidine is lower by that amount. However, the main contribution to the increase in the basicity of guanidine is found in substantially higher relaxation energy $E(\mathrm{ei})_{\mathrm{rex}}$, which assumes as large value as 28.5 kcal/mol. This is a consequence of the cationic resonance between three NH_2 groups in the protonated form. They symmetrically surround the carbocationic center and take planar conformation in order to maximize the resonance effect.

A large number of interesting acids and bases are analyzed and discussed recently[21,22]. An important outcome of these results is that Koopmans' ionization potentials play a very important role as a rule in determining basicity and acidity of molecules.

5 Concluding Remarks

A systematic study of the basicity of organic molecules has resulted in the Aufbau Prinzip for building up strong neutral superbases. This set of simple rules proved very useful in designing a very dense ladder of superbases, which extend up to PAs of 300 kcal/mol or higher, thus entering the region of strong mineral superacids. The most important effects used for this purpose are the cationic resonance effect, aromatization and aromatic domino

effects triggered by protonation. Very useful devices, either for fine tuning or for amplifying basicity, are provided by the substituent and IMHB corona effects. Since a similar work on a design of neutral organic superacids is completed, one can say that a strong overlapping of superacids and superbases is achieved in the region between 255 and 300 kcal/mol (Fig. 8). This is of importance since very close deprotonation energies of acids and PAs of bases are a prerequisite for a spontaneous proton transfer and formation of strong proton shared (almost symmetrical) hydrogen bonds. Hence, one can expect stable ion pairs exhibiting interesting features, which might lead to new materials with novel properties of high practical value.

Acknowledgments

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